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Original research

Evaluation of the effects of isotretinoin for treatment of acne on corneal sensitivity

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Abstract

Purpose: To determine the effect of isotretinoin on corneal sensitivity in acne patients.
Methods: Fifty patients (13 men and 37 women) with a mean age of 23.24 ± 3.4 years were selected among patients receiving isotretinoin (1.0 mg/kg) for acne according to inclusion criteria. The Cochet-Bonnet esthesiometer was used to measure corneal sensitivity (in mm filament length) two times (the measurements were done immediately before starting the medication, then 3 months after that), including 3 measurements each time, between 11 a.m. and 1 p.m. by an experienced operator. The average of the 3 measurements in each time was recorded as the final value. One-way analysis of variance and Chi square were used for quantitative and qualitative comparison of corneal sensitivity before and after isotretinoin use, respectively.
Results: The mean corneal sensitivity was 5.54 ± 0.05 before medication consumption which decreased to 5.41 ± 0.05 after isotretinoin treatment for 3 months ($P < 0.005$). After controlling the effect of age and sex, the decrease of corneal sensitivity was markedly significant ($P = 0.003$) as decreased corneal sensitivity was more pronounced at higher ages and in female gender. In non-parametric evaluation, corneal sensitivity was categorized as substantial (5.5–6 mm), intermediate (4.5–5.5 mm), and low (3.5–4.5). About 72% of the participants had substantial corneal sensitivity before drug consumption, which decreased to 60% after 3 months of treatment.
Conclusions: According to the results of this study, corneal sensitivity decreases after three months of treatment with isotretinoin. This decrease is more pronounced at higher ages and in women.

Keywords: Acne; Isotretinoin; Corneal sensitivity; Cochet-Bonnet esthesiometer

Introduction

A normal corneal sensitivity is important to the maintenance of normal corneal structure and function. Corneal sensitivity may markedly decrease in some ocular and systemic diseases, some physiological conditions, and following the use of certain drugs and ocular surgical procedures.[1] Aging, pregnancy, and eyelid occlusion for a long time are among the physiological conditions leading to decreased corneal sensitivity.[2,3] A number of pathological conditions

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such as dry eye, diabetes, myasthenia gravis, leprosy, corneal dystrophy, keratoconus, and trachoma also reduce corneal sensitivity.[4–6] Corneal innervation not only provides corneal sensitivity, but is also vital to the maintenance of corneal structure and function for preservation of corneal integrity and epithelial would healing following diseases, trauma, or surgery.[7] In fact, corneal nerves play an important role in protecting the cornea from stimuli and its nutrition.[8,9] According to the literature, corneal dryness is an important factor in decreased corneal sensitivity.[4,10,11] Certain medication such as isotretinoin, antihistamine, anticholinergics, and oral contraceptive pills cause dry eye.[12] Isotretinoin is now widely used for the treatment of acne.[13] Acne is a common skin inflammatory condition[14,15] affecting approximately 9.4% of the world's population, making it the 8th most common disease worldwide.[16] Different treatments have been proposed for different severities of acne. Regarding the fact that acne-generating microorganisms show resistance to conventional antibiotics,[17] oral isotretinoin is commonly used to treat this skin disease instead.[18] It should be noted that it is the only effective drug against all factors involved in acne.[19] The side effects of isotretinoin range from eyelid and corneal changes to lacrimal abnormalities resulting in dry eye.[20–22] Dry eye is the most common side effect associated with isotretinoin consumption which may be related to the atrophy of lacrimal glands and changes in the tear film quality.[23] There are reports of the effect of this medication on dry eye,[10] meibomian glands,[13] conjunctival goblet cells,[20] visual acuity,[22] retina,[24] intraocular pressure,[25] color vision,[26] and corneal topographic and biomechanical properties.[14]

Several studies have assessed the effect of dry eye on corneal sensitivity.[4,10,11] Given the widespread use of isotretinoin and the resulting dry eye following its use, it is a matter of debate whether this medication affects corneal sensitivity. Some systemic medications such as chloroquine and contraceptive pills decrease corneal sensitivity.[27] However, we found no evidence of the effect of isotretinoin on corneal sensitivity in the literature. The effect of the mentioned drugs on corneal sensitivity and the importance of corneal sensitivity in protecting the cornea from stimuli, corneal wound healing, corneal reflex, lacrimal flow, and maintenance of the corneal structure and health as well as the widespread use of isotretinoin encouraged us to investigate the effect of isotretinoin on corneal sensitivity in a well-designed study.

Methods

Fifty-eight individuals participated in this interventional prospective case series study. Five were excluded due to lack of cooperation to touching the Cochet-Bonnet filament with their eyes, and 3 were lost to follow-up, so our study continued with 13 men and 37 women. The statistical population of the study was individuals who visited a selected skin and hair clinic for acne, were 18–36 years old, received isotretinoin at a certain dose (1.0 mg/kg/day), did not receive eye drops during treatments with isotretinoin, and were willing to participate in the study. After coordination with the manager of the skin and hair clinic, informed consent was taken from all volunteers, and the protocol of the study was explained to them. The Ethics Committee of Iran University of Medical Sciences approved the study protocol, which was conducted in accord with the tenets of the Declaration of Helsinki. All participants signed a written informed consent.

The participants were selected based on the inclusion criteria (age 18–33 years, having acne, and taking isotretinoin as the only drug). The participants with systemic or ocular diseases (infections, allergies, dystrophies, injuries), positive history of ocular surgery, corneal scars, contact lens use, or severe dry eye were excluded from the study due to the effect of these conditions on corneal sensitivity. The method of corneal sensitivity measurement was explained to the participants, and they were assured that the test was harmless and painless. An experienced person measured corneal sensitivity in the corneal center using the Cochet-Bonnet esthesiometer. This esthesiometer works based on pressure applied vertically through a nylon filament with a diameter of 0.012 mm^2 and a length varying from 5 to 60 mm. Although the Cochet-Bonnet test is a standard clinical test for corneal sensitivity, a positive response mainly depends on the patient's perception and insight. Since other methods (air puff, chemical stimulation by capsaicin, and thermal stimulation by carbon dioxide laser) are expensive and difficult to carry around, the Cochet-Bonnet method is still the routine clinical method to measure corneal sensitivity with a high repeatability and reliability.[28] Certain precautions like regulation of humidity, temperature, and light were practiced to provide a similar condition for all measurements. Since studies have shown that corneal sensitivity is different at different times of the day,[29] all measurements were done at a specific time (between 11 a.m. and 1 p.m.) before and after drug use. Corneal sensitivity was measured three times in each eye, and the mean value of three measurements was recorded. The patient sat on a chair and looked straight forward. Using the handheld Cochet-Bonnet esthesiometer, a nylon monofilament with maximum length (60 mm) was slowly moved towards the corneal center vertically. Contact was determined by mild folding the filament (5% of its free length), and the patient was asked to report when (s)he felt its contact. If the patient was unable to feel the contact at full length, the filament was retracted incrementally in 0.5 mm steps until the contact of the filament with the central cornea was felt. The test was repeated three times, and the mean filament length when contact was felt was recorded as the corneal sensitivity threshold. The length was converted to pressure using a conversion table. Measurements were done for both eyes. Since no marked difference was observed between the results of the right and left eye of each patient, the mean value of both eyes was used for analysis. All measurements were done by one person. After measurements, the filament was sterilized with ethanol. After treatment with isotretinoin for 3 months at a dose of 1.0 mg/kg/day, corneal sensitivity was again measured in these patients.

The SPSS software was used to analyze the data of pre and post drug consumption. Considering the correlation between

the result of both eyes in terms of corneal sensitivity data, the Generalized Linear Models method of analysis was used.

However, because our sampling was rather discrete, and corneal sensitivity changed in 0.5 cm steps, the data seemed to be qualitative rather than quantitative.

Results

One hundred eyes of 50 volunteers (13 men and 37 women) with a mean age of 23.24 ± 3.4 years (18–33 years) were evaluated. The mean corneal sensitivity was 5.54 ± 0.05 mm before drug use which decreased to 5.41 ± 0.05 mm after treatment with isotretinoin for 3 months. Generalized Linear Models was used to compare corneal sensitivity before and after medication use, which showed a significant difference [$P = 0.002$; coef: 0.125 95% confidence intervals (CI): 0.046–0.204]; after controlling the effect of sex and age in corneal sensitivity showed a significant difference compared to the value before drug usage ($P < 0.001$).

After categorizing corneal sensitivity as low, moderate, and substantial, we found that 5%, 23%, and 72% of the patients had low, moderate, and substantial corneal sensitivity before medication consumption and 6%, 34%, and 60% of the patients had low, moderate, and substantial corneal sensitivity after medication used for three months, respectively. McNemar's test showed a significant difference before and after drug use ($P = 0.009$).

Discussion

Our prospective case series study showed a significant decrease in corneal sensitivity after using isotretinoin for 3 months. This decrease was more pronounced in women and at older ages. There is no evidence of decreased corneal sensitivity after isotretinoin consumption in the literature, but its adverse effects on the eye have been evaluated. Polat,[30] Miera,[31] Franfelder,[26] and Ayseoner[15] assessed the adverse effects of isotretinoin on the eye and reported decreased lacrimal flow and dry eye as the main adverse effects.

In 2016, Polat et al.[30] conducted a study on 25 patients (16 women and 9 men) who received oral isotretinoin to evaluate its effect on contrast sensitivity and lacrimal secretion. The treatment period was 4–7 months in this study, and the patients underwent Schirmer's test in both eyes before and after drug consumption. There was a significant decrease in the lacrimal flow after oral consumption of isotretinoin. Similarly, Karalezli reported a tear break up time (TBUT) of 12.84 s before treatment which decreased to 7.84 s 30 days after the start of treatment, indicating the development of dry eye after using the drug for one month.[32] In 2015, Mayo et al. evaluated the effect of isotretinoin on meibomian glands. Despite the normal appearance of the structure of meibomian glands in imaging studies, there were some signs of palpebral margin inflammation and decreased secretory function of these glands. Moreover, the symptoms of dryness largely affected the patients' quality of life.[13] However, the question is how isotretinoin affects corneal sensitivity. We found a marked decrease in the corneal sensitivity after treatment with isotretinoin for three months, but does the same mechanism causing dry eye decrease corneal sensitivity, as well? Some studies have shown that corneal sensitivity decreases as a result of dry eye.[4,10,11] Bourcier et al. conducted a study to evaluate corneal sensitivity in patients with dry eye in 2005. They included 44 patients with dry eye and 42 healthy subjects as the control group in their study and used the Belmonte's non-contact gas esthesiometer to measure corneal sensitivity in all participants. The results showed that dry eye patients had decreased corneal sensitivity to mechanical, chemical, and thermal stimulation as compared to the control group, probably due to decreased number of active nerve terminals as a result of pathological changes in corneal superficial layers. Therefore, dryness resulting from drug consumption could cause decreased corneal sensitivity.

In another study, Queiroga et al.[20] evaluated the effect of isotretinoin on conjunctival goblet cells after three months of isotretinoin treatment, and found that non-keratinized conjunctival epithelial cells were pathologically keratinized and transformed to non-secretory epithelial cells, resulting in a decrease in the number of mucin-producing goblet cells. Therefore, isotretinoin could decrease tear quality through interfering with mucin-production. We found no study ruling out the effect of isotretinoin on lacrimation; hence, it seems rational to conclude that isotretinoin consumption, in addition to causing dry eye, decreases corneal sensitivity. However, more studies are required to confirm whether or not dry eye leads to decreased corneal sensitivity. Furthermore, isotretinoin decreases lipid secretion by about 90% within 6 weeks through decreasing the size of meibomian glands and the number of sebocytes, and inhibiting lipid production.[33] Ding et al. found that isotretinoin altered the gene expression of meibomian gland epithelial cells, decreased the activity of cell survival mediators, inhibited cell proliferation, and increased cell death.[33] Since meibomian glands produce the lipid layer of the tear film, which is one of the main layers providing a smooth optical surface for the cornea and preventing tear evaporation,[34] it could be concluded that damage to the activity of meibomian glands results in decreased production of the tear film lipid layer, increased tear film evaporation, and dryness of the eye surface. In fact, dry eye following the use of isotretinoin is associated with pathologic changes of the meibomian glands rather than decreased function of lacrimal glands. It is believed that in people with dry eye, decreased corneal sensitivity is associated with disorders in the integrity of the ocular surface because corneal sensory nerves may adapt to decreased frequency and intensity of action potential. When nerve terminals are damaged, they lose their capability to transfer energy, leading to decreased number of healthy terminals capable of transmitting normal stimuli and increased number of damaged axons in different stages of frequency generation, resulting in abnormal impulses.[11] We noticed a decrease in corneal sensitivity following the use of isotretinoin, which was more pronounced in the female gender and at older ages.

The current study has its own strengths and weaknesses. The strength of our study is that so far, few studies have been conducted considering the effect of isotretinoin on corneal sensitivity. On the other hand, lack of control group, placebo effect, and the low sample size are considered to be the limitations of this study. Since the Cochet-Bonnet esthesiometer can only measure mechanical sensitivity of the cornea and suffers limitations in the sensitivity and repeatability of the measurements, and because we only evaluated corneal sensitivity after 12 weeks of treatment with isotretinoin due to time limitations, we also recommend doing in vivo confocal microscopy of corneal nerve for documenting corneal nerve damage by oral isotretinoin.

References

1. Stachs O, Zhivov A, Kraak R, Hovakimyan M, Wree A, Guthoff R. Structural-functional correlations of corneal innervation after LASIK and penetrating keratoplasty. *J Refract Surg*. 2010;26(3):159−167.
2. Roszkowska AM, Colosi P, Ferreri FM, Galasso S. Age-related modifications of corneal sensitivity. *Ophthalmologica*. 2004;218(5):350−355.
3. Millodot M. The influence of age on the sensitivity of the cornea. *Investig Ophthalmol Vis Sci*. 1977;16(3):240−242.
4. Xu KP, Yagi Y, Tsubota K. Decrease in corneal sensitivity and change in tear function in dry eye. *Cornea*. 1996;15(3):235−239.
5. Hieselaar LC, Hogeweg M, de Vries CL. Corneal sensitivity in patients with leprosy and in controls. *Br J Ophthalmol*. 1995;79(11):993−995.
6. Nazarian J, O'Leary D. Corneal sensitivity in myasthenia gravis. *Br J Ophthalmol*. 1985;69(7):519−521.
7. Tavakoli M, Petropoulos IN, Malik RA. Assessing corneal nerve structure and function in diabetic neuropathy. *Clin Exp Optom*. 2012;95(3):338−347.
8. Muller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res*. 2003;76(5):521−542.
9. Booranapong W, Tanthuvanit P, Suwannik A. Corneal sensitivity in normal Thai population. *Siriraj Med J*. 2005;57(7):4.
10. Bourcier T, Acosta MC, Borderie V, et al. Decreased corneal sensitivity in patients with dry eye. *Investig Ophthalmol Vis Sci*. 2005;46(7):2341−2345.
11. Hosal BM, Ornek N, Zilelioglu G, Elhan AH. Morphology of corneal nerves and corneal sensation in dry eye: a preliminary study. *Eye (Lond)*. 2005;19(12):1276−1279.
12. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. *Dtsch Arztebl Int*. 2015;112(5):71−81. quiz 82.
13. Moy A, McNamara NA, Lin MC. Effects of isotretinoin on meibomian glands. *Optom Vis Sci*. 2015;92(9):925−930.
14. Yildirim Y, Olcucu O, Agca A, et al. Evaluation of corneal topography and biomechanical parameters after use of systemic isotretinoin in acne vulgaris. *J Ophthalmol*. 2014;2014:701361.
15. Oner A, Ferahbas A, Karakucuk S, et al. Ocular side effects associated with systemic isotretinoin. *J Toxicol Cutan Ocul Toxicol*. 2005;23(3):189−195.
16. Tan JK, Bhate K. A global perspective on the epidemiology of acne. *Br J Dermatol*. 2015;172(Suppl 1):3−12.
17. Hassanzadeh P, Bahmani M, Mehrabani D. Bacterial resistance to antibiotics in acne vulgaris: an in vitro study. *Indian J Dermatol*. 2008;53(3):122−124.
18. Webster GF. Acne vulgaris. *Br Med J*. 2002;325(7362):475−479.
19. Layton A. The use of isotretinoin in acne. *Dermatoendocrinology*. 2009;1(3):162−169.
20. de Queiroga IB, Antonio Vieira L, Barros Jde N, Melo Diniz Mde F, de Morais LC. Conjunctival impression cytology changes induced by oral isotretinoin. *Cornea*. 2009;28(9):1009−1013.
21. Gomes JAP, Azar DT, Baudouin C, et al. TFOS DEWS II iatrogenic report. *Ocul Surf*. 2017;15(3):511−538.
22. Santodomingo-Rubido J, Barrado-Navascues E, Rubido-Crespo MJ. Drug-induced ocular side-effects with isotretinoin. *Ophthalmic Physiol Opt*. 2008;28(5):497−501.
23. Carr RE, Gouras P, Gunkel RD. Chloroquine retinopathy. Early detection by retinal threshold test. *Arch Ophthalmol*. 1966;75(2):171−178.
24. Lerman S. Ocular side effects of accutane therapy. *Lens Eye Toxic Res*. 1992;9(3-4):429−438.
25. Fraunfelder FT, Fraunfelder FW, Edwards R. Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol*. 2001;132(3):299−305.
26. Fraunfelder FT, Fraunfelder FW, Chambers WA. *Clinical Ocular Toxicology E-book: Drug-induced Ocular Side Effects*. Elsevier Health Sciences; 2008.
27. Decherney AH. The use of birth control pills in women with medical disorders. *Clin Obstet Gynecol*. 1981;24(3):965−975.
28. Murphy PJ, Lawrenson JG, Patel S, Marshall J. Reliability of the non-contact corneal aesthesiometer and its comparison with the Cochet-Bonnet aesthesiometer. *Ophthalmic Physiol Opt*. 1998;18(6):532−539.
29. du Toit R, Vega JA, Fonn D, Simpson T. Diurnal variation of corneal sensitivity and thickness. *Cornea*. 2003;22(3):205−209.
30. Polat M, Kukner S. The effect of oral isotretinoin on visual contrast sensitivity and amount of lacrimation in patients with acne vulgaris. *Cutan Ocul Toxicol*. 2017;36(1):35−38.
31. Neudorfer M, Goldshtein I, Shamai-Lubovitz O, Chodick G, Dadon Y, Shalev V. Ocular adverse effects of systemic treatment with isotretinoin. *Arch Dermatol*. 2012;148(7):803−808.
32. Karalezli A, Borazan M, Altinors DD, Dursun R, Kiyici H, Akova YA. Conjunctival impression cytology, ocular surface, and tear-film changes in patients treated with systemic isotretinoin. *Cornea*. 2009;28(1):46−50.
33. Ding J, Kam WR, Dieckow J, Sullivan DA. The influence of 13-cis retinoic acid on human meibomian gland epithelial cells. *Investig Ophthalmol Vis Sci*. 2013;54(6):4341−4350.
34. Mathers WD, Lane JA. Meibomian gland lipids, evaporation, and tear film stability. *Adv Exp Med Biol*. 1998;438:349−360.